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Neuronal intranuclear inclusion disease presenting with an MELAS-like episode in chronic polyneuropathy

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Neuronal intranuclear inclusion disease (NIID) exhibits diverse clinical phenotypes caused by the intronic repeat expansion of *NOTCH2NLC*.[1,2] An acute encephalopathic episode can manifest in some patients with NIID.[3,4] Herein, we report an NIID patient harboring a de novo $\{(GGA)_n(GGC)_n\}_n$ repeat expansion in *NOTCH2NLC*, who developed abrupt mitochondrial encephalomyopathy, lactic acidosis, and stroke-like (MELAS)-like episode in the 15-year course clinical diagnosed as chronic inflammatory demyelinating polyneuropathy (CIDP).

Case report

A 31-year-old woman developed slowly progressing muscle weakness and paresthesia in all extremities. Neurologic examination at 33 years of age revealed distal dominant muscle weakness with areflexia and abnormal deep sensations in all extremities without obvious cranial nerve involvement. A nerve-conduction study revealed sensorimotor polyneuropathy in all extremities (table e-1, links.lww.com/NXG/A335). Although clinical and electrophysiologic features met the diagnostic criteria for CIDP,[5] she showed limited response to immunotherapy. At 45 years, she abruptly started experiencing headaches, nausea, and eventually, loss of consciousness. Neurologic examination revealed left conjugate eye deviation, neck stiffness, and left hemiparesis. Blood analysis revealed an elevated blood lactate/pyruvate molar ratio (lactate: 2.1 mmol/L, pyruvate: 0.022 mmol/L, molar ratio: 91, normal range <25.8). Brain MRI showed abnormal hyperintensities in the right hemisphere on diffusion-weighted images (DWIs) (figure, A) and T2-weighted images (figure, B), with gadolinium enhancement not corresponding to the vascular distribution. Hyperperfusion on arterial spin labelling (figure, C), dilation of the right cerebral artery (figure, D), and elevated lactate peak on magnetic resonance spectroscopy (MRS) (figure, E) in the involved areas were also identified. She was diagnosed with MELAS and was administered IV levetiracetam, edaravone, and oral taurine. She gradually improved without residual cognitive disturbances. Neither histopathologic studies nor whole mitochondrial genome sequence analysis on muscle biopsy showed any specific findings for mitochondrial disease. At 47 years of age, a follow-up neurologic examination revealed bilateral miosis with sluggish response to light. Brain MRI revealed both gray and white matter hyperintensities on T2-weighted images corresponding to acute encephalopathic lesions (figure, F and G). However, there was no abnormal corticomedullary hyperintensity on DWI. Abdominal skin biopsy performed at 47 years of age and re-examination of the sural nerve sample at 35 years resulted in NIID diagnosis, demonstrating eosinophilic intranuclear inclusions surrounded by a halo and antiubiquitin and p62-immunoreactive intranuclear inclusions in fibroblasts, sweat gland cells (figure, H),

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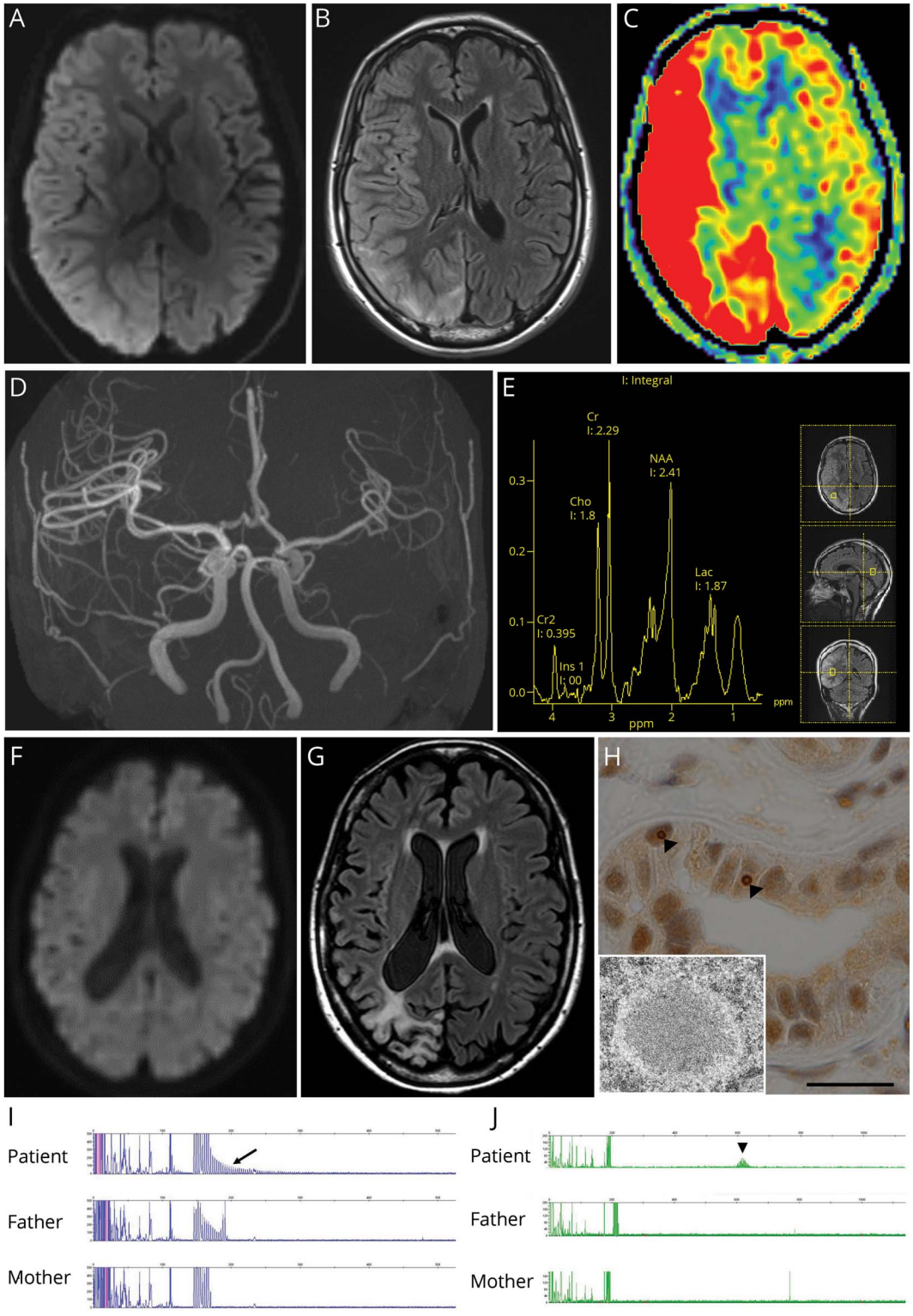
Figure Imaging, histopathologic, and genetic analyses of the patient



(A) DWI sequence shows hyperintensity around the right cortical and subcortical areas of parietal, temporal, and occipital lobes without corticomedullary hyperintensity. (B) FLAIR sequence shows hyperintensity and edematous areas in the right parietal, temporal, and occipital lobes. (C) ASL shows prominent hyperperfusion in accordance with the lesion. (D) MRA shows the dilation of right anterior, middle, and occipital cerebral arteries and of the right internal carotid artery. (E) MRS focused on the occipital lesion shows the lactate peak appearance. (F–G) MRI at 47 years of age (2 years after the MELAS-like episode). (F) DWI shows no corticomedullary junction DWI hyperintensity. (G) FLAIR shows leukoencephalopathy with atrophic changes in the occipital lobe. (H) Skin biopsy at the age of 47 years. Antiubiquitin positive intranuclear inclusions are seen in sweat glands (arrowheads) (scale bar = 20 μm). Electron microscopy of subcutaneous gland shows dense filamentous materials without limiting membrane (inset). (I) RP-PCR of the patient and her parents. Arrow shows a characteristic saw-tooth pattern in the patient. (J) Fluorescent repeat length analysis. GGC expansion is positive only in the patient. The expansion allele seen in the patient only is indicated as the arrowhead. ASL = arterial spin labeling; DWI = diffusion-weighted image; FLAIR = fluid-attenuated inversion recovery; MELAS = mitochondrial encephalomyopathy, lactic acidosis, and stroke; MRA = magnetic resonance angiography; MRS = magnetic resonance spectroscopy; RP-PCR = repeat-primed PCR; SPECT = single-photon emission CT.

adipocytes, perineural cells, fibroblasts, Schwann cells, and small vessels. Triobased whole exome sequencing resulted in negative results, confirming the biological parentage using 20 rare variants (data not shown). Presence of intranuclear inclusion bodies prompted to perform mutational analysis for detecting GGC trinucleotide expansion in *NOTCH2NLC*.[2] The trinucleotide repeat expansion was clearly visible in the patient, not in the parents, indicating a de novo mutation (figure, I and J). Long-read genomic sequencing and a cas9-enrichment system revealed a heterozygous intronic $(GGC)_{88}(GGGA)_1\{(GGC)_4(GGA)_2\}_9(GGC)_4(GGA)_1(GGC)_3(GGA)_2(GGC)_2$ repeat expansion in *NOTCH2NLC*.[2]

Discussion

We report a patient with NIID harboring a de novo intronic expansion containing $\{(GGA)_n(GGC)_n\}_n$ repeats in *NOTCH2NLC* presenting with a MELAS-like episode in long-standing chronic polyneuropathy mimicking CIDP. The genomic mechanism underlying a de novo mutation may be associated with the existence of expansion-prone sequences or structures within or surrounding the mutation site. Elevated serum lactate/pyruvate ratio and elevated lactate peak on MRS were strongly suggestive of MELAS, although the diagnosis was genetically ruled out. To date, only one NIID case presenting with MELAS-like phenotype and suggestive pathologic mitochondrial abnormalities has been reported.[6] Our case was unique in that an abnormal edematous and hyperemic brain lesion with elevated lactate peak was observed without typical corticomedullary DWI hyperintensity throughout the clinical course. Our case raised the possibility of mitochondrial dysfunction and effective therapeutic measures for mitochondrial diseases in acute encephalopathy associated with NIID.

Diverse phenotypes of NIID have been categorized into a dementia-dominant subtype typically with corticomedullary DWI hyperintense lesions and a weakness-dominant subtype predominantly with peripheral neuropathy.[3] A previous long-read repeat sequence analysis proposed a hypothesis that the insertion of $\{(GGA)_n(GGC)_n\}_n$ repeats causes a weakness-dominant subtype.[4] The complete repeat configurations in *NOTCH2NLC* of our case corroborated the hypothesis and supported the concept of "repeat motif-phenotype correlation."[7] Further accumulation of repeat configuration data is imperative to address whether specific repeat configurations are also associated with the MELAS-like episode.

In conclusion, NIID should be considered in the differential diagnosis of chronic sensorimotor neuropathy refractory to standard therapy and MELAS-like episodes lacking the characteristic brain MRI findings of NIID. This study provides mechanistic insight into NIID pathogenesis, implying that mitochondrial dysfunction might potentially be involved in acute encephalopathy associated with NIID and repeat configurations could be a key factor determining its phenotypes.

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Disclosure

The authors of this study declare no conflict of interest. The description in this paper has obtained informed consent from the patient. Go to Neurology.org/NG for full disclosures.

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Tasuku Ishihara, MD	National Center Hospital, National Center of Neurology and Psychiatry (NCNP), Tokyo, Japan	Clinical analysis and drafting and revising the manuscript
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Ken Saida, MD	Yokohama City University Graduate School of Medicine, Kanagawa, Japan	Genetic analysis
Yuji Saitoh, MD, PhD	National Center Hospital, NCNP, Tokyo, Japan	Clinical analysis and drafting and revising the manuscript
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Continued

Appendix *(continued)*

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Naomichi Matsumoto, MD, PhD	Yokohama City University Graduate School of Medicine, Kanagawa, Japan	Genetic analysis
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